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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/985,936	11/06/2001	Stefan Kappeler	KAPPELER=1A	4194

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09/26/2003

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, DC 20001

EXAMINER

RAMIREZ, DELIA M

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 09/26/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/985,936

Applicant(s)

KAPPELER ET AL.

Examiner

Delia M. Ramirez

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 July 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4-16 and 49-52 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4-16 and 49-52 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 08 July 2003 is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

Status of the Application

Claims 4-16 and 49-52 are pending.

Applicant's cancellation of claims 2-3, 35-40, amendment of claims 4, 7-8, 13, 15, 49, 51, and submission of a substitute declaration in Paper No. 13, filed on 7/8/2003 is acknowledged.

Applicants have affirmed the election of Group I with traverse. The traversal is on the ground(s) that because the DNA of Group I encodes the protein of Group II, it is not unduly burdensome to search both groups. While it is agreed that publications containing polynucleotide (Group I) information, such as open reading frame sequences, typically disclose the corresponding polypeptide (Group II), it is false to assume that the only source of information about a polypeptide is one in which polynucleotide information is disclosed. Therefore, the Examiner must search not only for polynucleotide but also for polypeptide information. In addition, a comprehensive search of each of the inventions would also require patented and non-patented literature searches, sequence searches and class/subclass searches. Thus, search of all inventions would impose an undue burden on the Office. The requirement is deemed proper and therefore is made FINAL.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Drawings

1. The drawings submitted on 7/8/2003 have been reviewed and are approved by a draftsperson under 37 CFR 1.84 or 1.152.

Claim Objections

2. Claim 50 is objected to because of the following informalities: for clarity, it is suggested that the term "host cell transferred with the DNA construct" be replaced with "host cell transformed with the DNA construct". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 4-16 and 49-52 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
5. Claim 8 is indefinite in the recitation of "a method according to claim 51 wherein the DNA differs from pGAMpR solely in that ..." for the following reasons. There is no antecedent basis for the term "DNA" or the term "pGAMpR". If the intended meaning of the term is "a method according to claim 51 wherein the DNA construct is plasmid pGAMpR except that said DNA construct comprises a different coding sequence", the claim should be amended accordingly. For examination purposes, the term will be interpreted as indicated above. Correction is required.
6. Claim 9 is indefinite in the recitation of "wherein the expression vector is pGAMpR-C" because there is no antecedent basis for the term "expression vector". If the intended meaning of the term is "wherein the DNA construct is the expression vector pGAMpRC", the claim should be amended accordingly. For examination purposes, the term will be interpreted as indicated above. Correction is required.
7. Claim 49 (claims 4-16 and 50-52 dependent thereon) is indefinite in the recitation of "fusion protein comprising a core protein which is such a pre-prochymosin, prochymosin or chymosin, and

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cleavable to release said core protein” for the following reasons. As written, the term “and cleavable” is unclear since one cannot determine what is “cleavable”. If the intended meaning of the term is “fusion protein comprising a core protein wherein said fusion protein is cleavable to release said core protein and wherein said core protein is a pre-prochymosin, prochymosin or chymosin of a mammal of the suborder Tylopoda”, the claim be amended accordingly. For examination purposes, the term will be interpreted as indicated above. Correction is required.

8. Claim 52 is indefinite in the recitation of “Camus” because it is unclear as to which genus is being referred to. If the intended genus is “Camelus”, the claim should be amended accordingly. For examination purposes, the term will be interpreted as “Camelus”. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 4-8, 10-11, 13-16 and 49-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection, which has been discussed at length in Paper No. 12, mailed on 4/8/2003, was applied to claims 4-8, 10-11, 13-16, 49-51 and is now applied to newly added claim 52 for the reasons of record.

11. Applicants argue that the specification discloses the active site of chymosin at page 1, lines 24-35. Also, Applicants argue that the present claims are not directed to non-naturally occurring mutants with a particular minimum sequence identity to camel chymosin, but rather to the expression of a naturally occurring non-bovine chymosin, prochymosin or preprochymosin. As such, Applicants argue

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that these proteins have chymosin activity by definition. Applicants submit that the skilled worker would consider where camel chymosin diverges from other bovine chymosins to determine the structural features which give camel chymosin superiority over bovine chymosin. Applicants assert that they are not concerned with non-naturally occurring chymosins but rather with identifying naturally occurring ones which share camel chymosin's superiority. According to Applicants, Bork teaches that prediction of functional features by homology is 90% accurate. Applicants argue that in general, the greater the degree of sequence similarity, the more likely they are to have the same activity. Applicants submit that alignment of sequences allows for identification of conserved and unconserved regions and that in the case of Witkowski et al., the researchers deliberately modified an amino acid residue of the active site. In view of the limitation of claim 49 to Tylopoda, Applicants conclude that this rejection should be withdrawn.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection in regard to claims 4-8, 10-11, 13-16 and 49-51, or avoid the rejection of newly added claim 52. While it is agreed that (1) the consensus motif of the active site of a chymosin has been disclosed, and (2) claim 49 is directed to DNA constructs comprising polynucleotides encoding Tylopoda pre-prochymosin, prochymosin, or chymosin, the Examiner disagrees with Applicant's contention that the limitation "Tylopoda" is sufficient to overcome the instant rejection. In order to adequately describe the claimed genus, structure as well as function is required for the genus of polynucleotides encompassed by the claims. The current written description guidelines indicate that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

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Therefore, to adequately describe the claimed genus, a representative number of species should be provided. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Amended claim 49 does not recite any structural limitation which correlates with the desired function. See *University of California v. Eli Lilly and Co.* (43 USPQ2d 1398). In addition, since the claimed invention is from an unpredictable art (see the teachings of Bork, Broun et al., Seffernick et al., Witkowski et al. and Van de Loo et al. already discussed), adequate written description of a genus which encompasses widely variant species cannot be achieved by disclosing only one species within the genus (i.e. the polynucleotide contained in deposits CBS 108915 and 108916).

The structural feature (i.e. a four amino acid motif) disclosed in the specification, while specific to the active site of chymosin domains, is not sufficient to adequately described the claimed genus since it is only a very small portion of the structure of a chymosin. Also, this structural feature does not provide any information as to what is required in a Tylopoda chymosin to be superior to bovine chymosin. In regard to Applicant's contention that one of skill in the art can identify naturally occurring chymosins which share chymosin's superiority by sequence comparison and that Bork (Genome Research, 10:398-400, 2000) teaches that prediction of functional features by homology is 90% accurate, it is noted that the 90% accuracy in Table 1 of Bork refers to prediction of accuracy in 70% of unicellular genomes and even Bork admits that the accuracy numbers in Table 1 are overestimates because the test sets used are usually not representative of all sequences (page 400, first column, last paragraph). Furthermore, while it is agreed that a high structural similarity would lead one of skill in the art to conclude that two proteins may share a similar activity, the Examiner has presented evidence which suggest that this assumption is not always correct. The Examiner agrees that one of skill in the art is more likely to expect greater activity changes if the active site is modified, as is the case in Witkowski et al., however, in the instant case, the

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specification is silent in regard to which structural elements are conserved (with the exception of the four amino acid motif), which ones are not conserved, and which conserved elements correlate with function. While alignment of different sequences can provide some information as to which structural elements are conserved, such alignment does not provide any information as to which of the conserved structural elements correlate with the desired function. Thus, in view of the insufficient description of the attributes and features of all species within the claimed genus, one cannot reasonably conclude that Applicants were in possession of the claimed invention at the time the instant application was filed.

13. Claims 4-8, 10-11, 13-16 and 49-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the DNA constructs present in the biological deposits CBS 108915 and CBS 108916, a host cell comprising said DNA constructs, and a method of producing the pre-prochymosin, prochymosin, or chymosin of said constructs, does not reasonably provide enablement for (1) a DNA construct comprising a polynucleotide which encodes any Tylopoda pre-prochymosin, prochymosin, or chymosin, (2) a method of recombinantly producing any Tylopoda pre-prochymosin, prochymosin, or chymosin, (3) a DNA construct comprising a polynucleotide which encodes any Camelus or Camelus dromedaries pre-prochymosin, prochymosin, or chymosin, or (4) a method of recombinantly producing any Camelus or Camelus dromedaries pre-prochymosin, prochymosin, or chymosin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection, which has been discussed at length in Paper No. 12, mailed on 4/8/2003, was applied to claims 4-8, 10-11, 13-16, 49-51 and is now applied to newly added claim 52 for the reasons of record.

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14. Applicants argue that given the present limitation in regard to tylopods, there is only a small number of pre-prochymosins, prochymosins and chymosins encompassed by the claims. As such, Applicants submit that this rejection should be withdrawn.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection in regard to claims 4-8, 10-11, 13-16 and 49-51, or avoid the rejection of newly added claim 52. While it is agreed that claim 49 has been amended to add the limitation "Tylopoda", the Examiner disagrees with Applicant's contention that the claims are enabled for their full scope since the number of pre-prochymosins, prochymosins and chymosins is small. The specification is silent in regard to the critical structural elements required in all Tylopoda pre-prochymosins, prochymosins, or chymosins. While it is agreed that the specification discloses a four amino acid motif, this structural element is one which is common to all chymosins and does not represent a substantial portion of a chymosin. Furthermore, the specification does not provide any information as to other Camelus dromedaries chymosins or allelic variants of the one encoded by the polynucleotide contained in deposits CBS 108915 or CBS 108916. The argument can be made that all the Tylopoda species encompassed by the claims should be highly homologous in structure. However, the specification does not provide any information as to which are the structural elements which are shared by all Tylopoda chymosins nor does it provide any information as to how much variation is found among all Tylopoda chymosins. Furthermore, the specification is silent in regard to which are the structural elements in any Tylopoda chymosin which are responsible for its improved milk clotting activity over bovine chymosin, or whether all Tylopoda chymosins are superior to bovine chymosins. As indicated previously, the state of the art is unpredictable in regard to assigning function based on structural homology as evidenced by Bork, Broun et al., Van de Loo et al., Seffernick et al. and Witkowski et al. already discussed. Therefore, in view of the information provided, the lack of relevant examples, and the unpredictability of the art in regard to assigning function

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based on structural homology, one of skill in the art would have to go through the burden of undue experimentation to enable the full scope of the claims.

16. Claims 9 and 12 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

17. This rejection was applied since there was no indication in the specification as to public availability. In view of Applicant's response (page 7, last paragraph-page 8, line 21) indicating that the biological deposits were deposited under the Budapest Treaty and will be irrevocably and without restriction or condition released to the public upon the issuance of a patent on this application, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 102

18. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

19. Claims 49-51, 5, 7, and 10 were rejected under 35 U.S.C. 102(b) as being anticipated by Nomura et al. (Appl. Microbiol. Biotechnol. 42:865-870, 1995). This rejection has been discussed at length in Paper No. 12, mailed on 4/8/2003.

20. Applicant's amendment of claims 49, 51 and 7, which are now directed to a DNA construct comprising a Tylopoda polynucleotide encoding a pre-prochymosin, prochymosin, chymosin, or fusion protein thereof, or a method to recombinantly produce such pre-prochymosin, prochymosin, chymosin or fusion thereof using said DNA construct, is deemed sufficient to overcome the rejection. Nomura et al. does not teach a Tylopoda polynucleotide encoding pre-prochymosin, prochymosin, chymosin, or fusion

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protein thereof, nor does it teach a method to recombinantly produce a Tylopoda protein. Thus, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

21. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
22. Claims 5-8, 10-11 and 49-51 were rejected under 35 U.S.C. 103(a) as being unpatentable over Houen et al. (Int. J. Biochem. Cell Biol. 28(6):667-675, 1996; cited in the IDS) in view of Ward et al. (Bio/Technology 8:435-440, 1990; cited in the IDS). This rejection has been discussed at length in Paper No. 12, mailed on 4/8/2003.
23. Claims 5-8, 10-11 and 49-51 were rejected under 35 U.S.C. 103(a) as being unpatentable over Pungercar et al. (Nucleic Acids Research 18(15):4602, 1990) in view of Ward et al. (Bio/Technology 8:435-440, 1990; cited in the IDS). This rejection has been discussed at length in Paper No. 12, mailed on 4/8/2003.
24. Amended claims 49, 51, 7 and 8 are now directed to a DNA construct comprising a Tylopoda polynucleotide encoding a pre-prochymosin, prochymosin, chymosin, or fusion protein thereof, or a method to recombinantly produce such pre-prochymosin, prochymosin, chymosin or fusion thereof using said DNA construct. Neither Houen et al., Pungercar et al. or Ward et al., individually or in combination, teach a Tylopoda polynucleotide encoding pre-prochymosin, prochymosin, chymosin, or fusion protein thereof, nor do they teach a method to recombinantly produce a Tylopoda protein. Thus, this rejection is hereby withdrawn.

Conclusion

25. No claim is in condition for allowance.

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26. Applicant's amendment of claims 4, 7-8, 13, 15, 49, 51 and addition of claim 52, necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

27. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED**, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 22, 2003

Rebecca E. Proby
REBECCA E. PROBY
PRIMARY EXAMINER
GROUP 1000
1600